

Visceral Adiposity and the Prevalence of Hypertension in Japanese Americans

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Background—Visceral adiposity is generally considered to play a key role in the metabolic syndrome, including hypertension. The purpose of this study was to evaluate cross-sectionally whether visceral adiposity is associated with prevalence of hypertension independent of other adipose depots and fasting plasma insulin.

Methods and Results—Study subjects included 563 Japanese Americans with normal or impaired glucose tolerance or diabetes but not taking oral hypoglycemic medication or insulin at entry. Variables included plasma glucose and insulin measured after an overnight fast and during an oral glucose tolerance test, and abdominal, thoracic, and thigh fat areas by CT. Total fat area (TFA) was calculated as the sum of these fat areas. Hypertension was defined as having a systolic blood pressure ≥ 140 mm Hg, having a diastolic blood pressure ≥ 90 mm Hg, or taking antihypertensive medications. Intra-abdominal fat area (IAFA) was associated with a higher prevalence of hypertension. Adjusted odds ratio of hypertension by IAFA was 1.68 for a 1-SD increase (95% CI, 1.20 to 2.37) after adjusting for age, sex, fasting plasma insulin, a nonlinear transformation of 2-hour plasma glucose, and TFA. IAFA remained a significant predictor of prevalence of hypertension even after adjustment for total subcutaneous fat area, abdominal subcutaneous fat area, body mass index, or waist circumference, but no measure of regional or total adiposity was associated with the odds of prevalence of hypertension in models that contained IAFA.

Conclusions—Greater visceral adiposity increases the odds of hypertension in Japanese Americans independent of other adipose depots and fasting plasma insulin. (*Circulation*. 2003;108:1718-1723.)

Key Words: epidemiology ■ hypertension ■ visceral fat ■ obesity ■ risk factors

Metabolic syndrome is the cluster of obesity, insulin resistance, hyperinsulinemia, dyslipidemia, glucose intolerance, and hypertension.¹ A central pattern of body fat distribution is now generally considered to play an important role in this syndrome. In particular, visceral adiposity has been reported to play a key role in these diseases compared with other measurements of regional or generalized obesity.²⁻⁴ But not known is whether visceral adiposity directly measured by CT increases the odds of hypertension, independent of other adipose depots, and insulin resistance.

Previous research on the association between greater central obesity, measured by the ratio of waist-to-hip circumference, or the ratio of subscapular to triceps skinfold thickness and the risk of hypertension were inconclusive.⁵⁻⁹ In these studies, controlling for other potentially confounding variables such as insulin resistance was not performed, subjects with borderline hypertension were classified as having normotension, or the definition of hypertension was not clear. The contribution of visceral fat was not distinguished from that of subcutaneous abdominal fat. Only limited cross-

sectional data are available on relating visceral adiposity directly measured by CT to blood pressure. Two studies have reported a significant or borderline significant association,^{2,10} but one study has reported a null association.¹¹ Differences in exclusion criteria, age distribution of study subjects, or the method of enrolling subjects may explain the inconclusive associations. In the present study, we therefore examined the relationship between directly measured visceral adiposity and the odds of hypertension independent of other measurements of total and regional adiposity and fasting plasma insulin.

Methods

Study Population

The study population consisted of second- and third-generation (mean age, 49.5 ± 11.8 years) Japanese Americans with normal (NGT) or impaired glucose tolerance (IGT) or diabetes but not taking oral hypoglycemic medications or insulin, who were enrolled in the Japanese-American Community Diabetes Study. Details about selection and recruitment of the sample population have been described previously.^{12,13}

Received December 17, 2002; de novo received May 16, 2003; accepted June 16, 2003.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000087597.59169.8D

TABLE 1. Characteristics of Study Subjects According to Hypertension Status

Characteristics	Total (n=563)	Normotension (n=360)	Hypertension (n=203)	Crude OR (95% CI)	P
Age (years)	53.0±11.9	49.5±11.8	59.3±9.4	2.55 (2.07–3.14)	<0.001
Female sex (%)	45.6	49.7	38.4	0.63 (0.45–0.90)	0.010
Metabolic variables					
Fasting plasma insulin (pmol/L)	83.5±45.9	76.8±37.8	95.4±55.8	1.45 (1.25–1.79)	<0.001
Fasting plasma glucose (mmol/L)	5.46±1.26	5.26±1.15	5.81±1.36	1.64 (1.32–2.05)	<0.001
2hPG (mmol/L)	8.23±3.39	7.55±2.97	9.43±3.76	...*	...*
2hPG model [$\log_e(2hPG) - 0.0588(2hPG)$]†	2.23 (1.79–2.78)	<0.001
Adipose variables					
IAFA (cm ²)	86.9±52.5	71.2±44.5	114.7±54.3	2.53 (2.05–3.12)	<0.001
Abdomen subcutaneous fat area (cm ²)	157.9±75.2	150.6±72.5	170.8±75.8	1.31 (1.10–1.55)	0.003
Total subcutaneous fat area (cm ²)	391.1±171.6	381.1±172.0	408.8±170.0	1.17 (0.99–1.39)	0.067
TFA (cm ²)	478.0±195.2	452.3±193.4	523.5±190.4	1.44 (1.21–1.72)	<0.001
BMI (kg/m ²)	24.3±3.3	23.7±3.1	25.3±3.5	1.62 (1.35–1.94)	<0.001
Waist circumference (cm)	86.3±8.8	84.4±8.1	89.7±8.9	1.92 (1.57–2.33)	<0.001

Data are mean±SD or %. ORs for continuous variables reflect a 1-SD-magnitude increase. Total subcutaneous fat area and TFA represent sums of adipose tissue areas as determined by multiple CT slices. P value is for univariate logistic regression analyses.

*See model below (†).

†2hPG model= $\log_e(2hPG) - \beta_1/\beta_2 \times (2hPG)$; β_1 and β_2 denote coefficients of 2hPG and $\log_e(2hPG)$, respectively; $\beta_1 = -0.283$, $\beta_2 = 4.815$. \log_e denotes natural logarithm.

Data Collection

All evaluations were performed at the General Clinical Research Center, University of Washington. The protocol for this research was reviewed by the Human Subjects Review Committee at the University of Washington, and signed, informed consent was obtained from all participants. An average blood pressure was calculated from the second and third of 3 consecutive measurements with a mercury sphygmomanometer read to the nearest 2 mm Hg with the patient in the recumbent position. Systolic blood pressure was determined by the first perception of sound and the diastolic fifth phase blood pressure at Korotkoff sound disappearance. Hypertension was defined as having a systolic blood pressure ≥ 140 mm Hg, having a diastolic blood pressure ≥ 90 mm Hg, or taking antihypertensive medications. A 75-g oral glucose tolerance test was used to classify all subjects as having NGT, IGT, or type 2 diabetes based on the American Diabetes Association 1997 criteria.¹⁴ Plasma glucose was assayed by an automated glucose oxidase method. Fasting plasma insulin was measured by radioimmunoassay as reported previously.^{3,4}

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Single CT scans were obtained of the thorax, abdomen, and right thigh to measure fat areas (cm²) as described previously.¹⁵ Visceral adiposity was measured as intra-abdominal fat area (IAFA) at the umbilicus level. This measurement has been reported to have a high correlation with directly ascertained total visceral fat volume by CT or magnetic resonance image.^{16,17} Subcutaneous fat area was also measured by CT scans of the thorax, abdomen, and right thigh. Total fat area (TFA) was calculated as the sum of IAFA and thorax and subcutaneous abdominal fat areas, and twice the right thigh subcutaneous fat area. In research that we have previously conducted, TFA correlates highly with fat mass as measured by hydrodensitometry among Japanese Americans ($r=0.89$ to 0.94 ; M.J. McNeely, unpublished data, 1999). Total subcutaneous fat area was defined as TFA minus IAFA. Waist circumference was measured at the level of the umbilicus to the nearest tenth centimeter.

Statistical Analysis

Multiple logistic regression analysis was used to estimate the odds ratio (OR) for hypertension presence in relation to an increase of 1

SD in baseline variables. Nonlinear effects of continuous independent variables were evaluated using quadratic and log transformations. The presence of an effect modification was tested by the insertion of first-order interaction terms into appropriate regression models. We calculated the 95% confidence interval for each OR. Probability values are 2 tailed. Statistical analyses were performed using the SPSS version 10.0 software package (SPSS Inc).

Results

Among the 563 eligible men and women, we confirmed 203 cases of hypertension. In univariate logistic regression analysis, IAFA, abdominal subcutaneous fat area, TFA, BMI, and waist circumference, but not total subcutaneous fat area, were associated with a higher prevalence of hypertension. Age, male sex, fasting plasma insulin, fasting plasma glucose, and 2-hour plasma glucose (2hPG) were also associated with higher prevalence of hypertension (Table 1).

The crude prevalence of hypertension according to tertiles of regional or total adiposity, fasting plasma insulin, and gender is shown in Table 2. All regional fat areas, total adiposity, fasting plasma insulin, and gender were associated with prevalence of hypertension. After subjects were stratified according to tertiles of TFA, subcutaneous abdominal fat area, total subcutaneous fat area, BMI, waist circumference, fasting plasma insulin, or gender, greater visceral adiposity was found to be associated with a higher prevalence of hypertension in all groups (Table 2). On the other hand, after subjects were stratified according to IAFA, no measure of regional or total adiposity other than IAFA, fasting plasma insulin, or gender was found to be associated with prevalence of hypertension (Table 2).

To assess the effect of IAFA on prevalence of hypertension independent of glycemic status, subjects were dichotomized by diabetes status (defined as hyperglycemia [IGT or type 2 diabetes] or NGT) (Table 3). In both categories, greater

TABLE 2. Prevalence of Hypertension According to IAFA, TFA, Abdominal Subcutaneous Fat Area, Total Subcutaneous Fat Area, BMI, Waist Circumference, Fasting Plasma Insulin, and Gender

	Tertiles of IAFA			<i>P</i> for Trend	Total
	Tertile 1	Tertile 2	Tertile 3		
Total	33/187 (17.6)	55/188 (29.3)	115/188 (61.1)	<0.001	203/563 (36.1)
Tertiles of TFA					
Tertile 1	21/118 (17.8)	16/57 (28.1)	10/12 (83.3)	<0.001	47/187 (25.1)
Tertile 2	10/53 (18.9)	20/64 (31.3)	40/71 (56.3)	<0.001	70/188 (37.2)
Tertile 3	2/16 (12.5)	19/67 (28.4)	65/105 (61.9)	<0.001	86/188 (45.7)
<i>P</i> for trend	0.750	0.968	0.802		<0.001
Tertiles of abdomen subcutaneous fat area					
Tertile 1	20/107 (18.7)	16/49 (32.7)	19/31 (61.3)	<0.001	55/187 (29.4)
Tertile 2	10/58 (17.2)	17/63 (27.0)	40/67 (59.7)	<0.001	67/188 (35.6)
Tertile 3	3/22 (13.6)	22/76 (28.9)	56/90 (62.2)	<0.001	81/188 (43.1)
<i>P</i> for trend	0.586	0.770	0.822		0.006
Tertiles of total subcutaneous fat area					
Tertile 1	18/94 (19.1)	17/59 (28.8)	21/34 (61.8)	<0.001	56/187 (29.9)
Tertile 2	10/64 (15.6)	16/54 (29.6)	45/70 (64.3)	<0.001	71/188 (37.8)
Tertile 3	5/29 (17.2)	22/75 (29.3)	49/84 (58.3)	<0.001	76/188 (40.4)
<i>P</i> for trend	0.584	0.755	0.816		0.042
Tertiles of BMI					
Tertile 1	23/122 (18.9)	17/53 (32.1)	9/12 (75.0)	<0.001	49/187 (26.2)
Tertile 2	9/54 (16.7)	24/76 (31.6)	29/58 (50.0)	<0.001	62/188 (33.0)
Tertile 3	1/11 (9.1)	14/59 (23.7)	77/118 (65.3)	<0.001	92/188 (48.9)
<i>P</i> for trend	0.437	0.304	0.281		<0.001
Waist circumference					
Tertile 1	23/136 (16.9)	15/45 (33.3)	2/4 (50.0)	0.009	40/185 (21.6)
Tertile 2	9/44 (20.5)	22/83 (26.5)	33/62 (53.2)	<0.001	64/189 (33.9)
Tertile 3	1/6 (16.7)	18/59 (30.5)	80/122 (65.6)	<0.001	99/187 (52.9)
<i>P</i> for trend	0.695	0.833	0.095		<0.001
Fasting plasma insulin					
Tertile 1	16/93 (17.2)	12/46 (26.1)	19/34 (55.9)	<0.001	47/173 (27.2)
Tertile 2	14/76 (18.4)	24/73 (32.9)	34/57 (59.6)	<0.001	72/206 (35.0)
Tertile 3	3/18 (16.7)	19/69 (27.5)	62/97 (63.9)	<0.001	84/184 (45.7)
<i>P</i> for trend	0.968	0.887	0.389		<0.001
Gender					
Male	14/66 (21.2)	26/103 (25.2)	85/137 (62.0)	<0.001	125/306 (40.8)
Female	19/121 (15.7)	29/85 (34.1)	30/51 (58.8)	<0.001	78/257 (30.4)
<i>P</i> for χ^2 test	0.345	0.183	0.687		0.010

Data are n (%). Linear trends were evaluated by using the median value for each category in logistic regression analyses.

visceral adiposity was associated with a higher prevalence of hypertension (Table 3). Furthermore, after subjects were stratified by IAFA tertile, subjects with IGT or type 2 diabetes had a higher prevalence of hypertension than those with NGT in each IAFA category (Table 3).

In multiple logistic regression analysis, insertion of quadratic or log transformations of all variables except 2hPG into all models of Table 4 did not improve their fit compared with the linear model. Because both the linear and the log transformation of 2hPG were significant in all models at $P < 0.05$, both of these variables were retained in all models that included 2hPG. We examined the significance of the

first-order interaction terms in all models of Table 4 between IAFA, TFA, subcutaneous abdominal fat area, total subcutaneous fat area, BMI, or waist circumference and the other variables. None of these interactions was significant.

A number of regression models were tested to assess the effects of body fat distribution on prevalence of hypertension (Table 4). After adjusting for age, sex, fasting plasma insulin, 2hPG, log transformation of 2hPG, and TFA, IAFA was associated with prevalence of hypertension (model 1, Table 4). Model 2 of Table 4 was identical to model 1, with the exception that quintiles of 2hPG were used in place of 2hPG and log transformation of 2hPG to make it easily understood.

TABLE 3. Prevalence of Hypertension According to IAFA and Diabetes Status

	Diabetes Status		P for χ^2 Test
	NGT	IGT or Type 2 Diabetes	
Total	73/306 (23.9)	130/257(50.1)	<0.001
IAFA			
Tertile 1	19/135 (14.1)	14/52 (26.9)	0.039
Tertile 2	23/104 (22.1)	32/84 (38.1)	0.017
Tertile 3	31/67 (46.3)	84/121 (69.4)	0.002
P for trend	<0.001	<0.001	
Waist circumference			
Tertile 1	17/123 (13.8)	23/62 (37.1)	<0.001
Tertile 2	28/106 (26.4)	36/83 (43.4)	0.014
Tertile 3	28/75 (37.3)	71/112 (63.4)	<0.001
P for trend	<0.001	<0.001	

Data are n (%). Linear trends were evaluated by using the median value for each category in logistic regression analyses.

Models 3 to 6 of Table 4 were identical to model 2, with the exception that a different adiposity variable was used in place of TFA. Model 7 of Table 4 contained diabetes status in place of quintiles of 2hPG. In all of these models, the association between IAFA and prevalence of hypertension did not change appreciably (models 2 to 7, Table 4). Also, none of the other measures of regional or total adiposity emerged as significantly related to prevalence of hypertension (models 1 to 7, Table 4). Fasting plasma insulin, age, and 2hPG or diabetes status were also associated with a significantly increased prevalence of hypertension in all models of Table 4.

Discussion

These cross-sectional data demonstrated that greater visceral adiposity was associated with a higher prevalence of hypertension. This finding was independent of other measures of total and regional adiposity, fasting plasma insulin, 2hPG, age, and sex. On the other hand, no other measure of regional or total adiposity was associated with prevalence of hypertension after adjusting for IAFA.

A few epidemiological studies relating CT-measured IAFA to blood pressure were inconclusive.^{2,10,11} Kanai et al¹⁰ showed that, among severely obese women in Japan, the ratio of the IAFA to subcutaneous fat area measured by CT was related with blood pressure independent of age and BMI. Because this study focused on severely obese women who consulted their clinic for weight reduction, their results may not apply to the general population. Johnson et al¹¹ showed that, among subjects without diabetes and hypertension, CT-measured IAFA was not correlated with systolic and diastolic blood pressure. This study focused on relatively young men (mean age, 36 years). A 1995 publication, by our group, of cross-sectional data in Japanese Americans demonstrated that, among subjects without type 2 diabetes and not taking antihypertensive medication, the effects of visceral adiposity measured by CT on systolic or diastolic blood pressure were of statistical significance or borderline statis-

TABLE 4. Multivariate Models of Prevalence of Hypertension in Relation to Baseline Values of IAFA, Other Adipose Depots, and Fasting Plasma Insulin

Model and Variables in the Model	OR (95% CI)	P
Model 1		
IAFA	1.68 (1.20–2.37)	0.003
TFA	0.84 (0.60–1.15)	0.274
Fasting plasma insulin	1.49 (1.18–1.90)	0.001
Age	2.25 (1.74–2.92)	<0.001
Female sex	0.84 (0.48–1.46)	0.529
2hPG model [$\log_e(2hPG)-0.0781(2hPG)$]*	1.41 (1.10–1.81)	0.007
Model 2: same variables as in model 1, except quintiles of 2hPG are substituted for 2hPG		
IAFA	1.67 (1.19–2.35)	0.003
Quintiles of 2hPG		
Quintile 1 (2.66–5.94)	1.00 (reference)	
Quintile 2 (5.95–6.94)	1.31 (0.62–2.77)	0.482
Quintile 3 (6.95–8.05)	1.72 (0.83–3.57)	0.146
Quintile 4 (8.06–9.83)	2.21 (1.07–4.58)	0.033
Quintile 5 (9.84–32.86)	2.21 (1.04–4.72)	0.040
Model 3: same variables as in model 2, except abdominal subcutaneous fat area is substituted for TFA		
IAFA	1.53 (1.16–2.04)	0.003
Abdominal subcutaneous fat area	0.96 (0.74–1.23)	0.738
Model 4: same variables as in model 2, except total subcutaneous fat area is substituted for TFA		
IAFA	1.60 (1.20–2.15)	<0.001
Total subcutaneous fat area	0.87 (0.66–1.16)	0.339
Model 5: same variables as in model 2, except BMI is substituted for TFA		
IAFA	1.48 (1.09–2.00)	0.012
BMI	1.04 (0.77–1.39)	0.817
Model 6: same variables as in model 2, except waist circumference is substituted for TFA		
IAFA	1.44 (1.05–1.98)	0.024
Waist circumference	1.07 (0.79–1.45)	0.682
Model 7: same variables as in model 1, except diabetes status is substituted for 2hPG		
IAFA	1.70 (1.21–2.39)	0.001
Diabetes status		
NGT	1.00	
IGT or type 2 diabetes	1.65 (1.09–2.49)	0.018

ORs for continuous variables reflect a 1-SD–magnitude increase. *2hPG model= $\log_e(2hPG)-\beta_1/\beta_2 \times (2hPG)$; β_1 and β_2 denote coefficients of 2hPG and $\log_e(2hPG)$, respectively; $\beta_1 = -0.220$, $\beta_2 = 2.816$. \log_e denotes natural logarithm.

tical significance, independent of age and fasting plasma insulin, using multiple regression analyses.² But after further adjustment for BMI, these associations were diminished.² In that study, we did not include subjects taking antihyperten-

sive medication or having type 2 diabetes, which, by possibly truncating the upper range for blood pressure, may have underestimated these relationships in our previous publication in 1995.² To our knowledge, the present study is the first cross-sectional study to evaluate the relation of directly measured visceral adiposity to hypertension prevalence independent of other measures of total and regional adiposity and fasting plasma insulin.

Although reports of the association between fasting plasma insulin and hypertension have overall been inconsistent,^{7,8,11} this association was significant in the present study (Table 4). The presence of this association in our data varied depending on which covariates were included in our models. Fasting insulin significantly predicted hypertension in a univariate model but, after adjusting for IAFA, this effect was absent (data not shown), as can also be seen in Table 2. A similar negative association was seen after adjustment for IAFA, sex, TFA, and quintiles of 2hPG (data not shown). However, after further adjustment for age, the association re-emerged to a significant degree (Table 4). The first-order interaction between fasting plasma insulin and age in this final model was not significant. This finding argues for the importance of age adjustment in examining associations between fasting plasma insulin, IAFA, and hypertension.

Although the present study did not identify why visceral fat increases the risk of hypertension, a plausible mechanism may be at least in part based on the central role of insulin resistance.^{18,19} In the present study, adjustment for fasting plasma insulin did not remove a significant correlation between IAFA and prevalence of hypertension. Furthermore, this association was independent of total body fat and regional fat depots. Therefore, visceral adiposity may have effects on hypertension through mechanisms unrelated to insulin level or sensitivity. Recently, increased levels of plasminogen activator inhibitor-1, which is a major circulating inhibitor of thrombolysis, have been reported to be positively related to systolic blood pressure and diastolic blood pressure in the Framingham Offspring Study.²⁰ Interestingly, some studies have reported that visceral fat produced considerably more of this peptide than did subcutaneous fat.²¹ Therefore, plasminogen activator inhibitor-1 may have a key role relating visceral fat to the risk of hypertension. The role of body fat depots in the pathogenesis of hypertension requires further investigation.

There are several potential limitations to our study. First, we cannot draw conclusions about cause-and-effect relationships because of the cross-sectional nature of our data. Second, we used the sum of the areas of a limited number of CT scans to estimate total body fat mass. However, our group has found that this measurement correlates highly with fat mass as measured by hydrodensitometry among Japanese Americans ($r=0.89$ to 0.94). Visceral fat volume was also estimated with a single CT scan at the L4–L5 level. This measurement has been reported to have a high correlation with directly ascertained total visceral fat volume.^{16,17} Third, because we studied a single ethnic group, our results may not be representative of the general population. Some studies have reported ethnic group differences in the amount of visceral fat volume.²² Compared with white subjects, Asians

have been reported to have a higher and African Americans a lower visceral fat volume.²³ Given differences in visceral fat volume by ethnicity, there may also exist ethnic differences in the association between hypertension and visceral adiposity.

In conclusion, the present results provide evidence that visceral fat is a significant correlate of hypertension among Japanese Americans. This association is independent of fasting plasma insulin, which suggests that the effect of visceral fat on prevalence of hypertension may be mediated by processes not reflected by fasting plasma insulin. The mechanism by which visceral fat is associated with a higher prevalence of hypertension remains to be determined. Further prospective research would help to establish the temporal sequence between visceral fat volume and subsequent risk of hypertension.

Acknowledgment

This work was supported by NIH grants DK-31170, HL-49293, and DK-02654; by facilities and services provided by the Diabetes and Endocrinology Research Center (DK-17047), Clinical Nutrition Research Unit (DK-35816), and General Clinical Research Center (RR-00037) at the University of Washington; and by the Medical Research Service and Cooperative Studies Program of the Department of Veterans Affairs. We gratefully acknowledge the skilled assistance of staff members, especially Jane Shofer. We are grateful to the King County Japanese-American Community for support and cooperation.

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